REMARKS

Claims 15-24, 26, 29, 30, 32-38, 40 and 42-44 were pending in this application. Claims 15-22, 29 and 30 are amended herein. Claims 31-33 and 35-44 are canceled herein. New Claims 45-48 are added herein.

The claims have been amended in response to the finality of the restriction requirement in the current office action. While Applicants continue to disagree with the restriction requirement as set out in the office action filed 3/23/04, in order to expedite prosecution to allowance, the subject matter not in Group I as defined in the 3/23/04 office action has been deleted from the claims, without prejudice to claiming said subject matter in a continuing patent application.

The amendments herein are fully supported in the specification as filed, so that no new matter has been added. The amendments are not made for substantive reasons related to patentability. To the extent that the amendments may avoid the prior art, competitors are warned that the amendments are not intended to and do not limit the scope of equivalents which may be asserted on subject matter outside the literal scope of any patented claims but not anticipated or rendered obvious by the prior art or otherwise unpatentable to applicants.

Objections to the Claims

Claims 35, 36, 42, 43, and 44 have been objected to for various reasons. In view of the cancellation of these claims, these objections are now moot.

Rejection under 35 U.S.C. §112, 1¶

The Examiner has rejected Claims 15-24, 26, 29, 30, 32-38, 40 and 42-44 under 35 U.S.C. §112, 1¶ as failing to comply with the enablement requirement. In particular, the Examiner states that "...the specification does not reasonably provide enablement for a method of treating a patient suffering from chronic inflammation or a disease associated with chronic inflammation with the instant compounds.... The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims." As support for this rejection the Examiner lists the 8 well-known factors set forth in the Federal Circuit decision *In re Wands*, 8 USPQ 2d, 1400 (Fed. Cir. 1988).

Applicants respectfully traverse this rejection for at least the following reasons.

The enablement requirement of the first paragraph of 35 U.S.C. 112 requires that the patent specification enable those skilled in the art to make and use the full scope of the claimed

invention without *undue* experimentation based on the underlying facts. Applicants respectfully submit that the specification clearly enables one skilled in the art to use all of the compounds of formula I and formula II without undue experimentation.

As set forth in the USPTO's Training Materials for Examining Patent Applications with respect to 35 U.S.C. 112 Section 112, First Paragraph – Enabled Chemical/Biotechnical Applications ("Training Materials"), 35 U.S.C. 112 ¶1 requires that a specification explain how to make and use the invention as claimed in sufficient detail as to enable any person skilled in the art to make and use the invention as claimed **without undue experimentation**.

The specification teaches how to use the compounds of the invention. See, for example, pages 28, 34-35 and 40-41 where the compounds of the invention are disclosed as inhibitors of microglia activation and are therefore useful in treating disease-states, such as those characterized by chronic inflammation, that exhibit a chronic microglia activation. Also disclosed at pages 40-41 are various assays which would enable one skilled in the art on how to use the compounds for the intended use. In addition, the specification discloses in Examples 307, 308 and 309 specific assay protocols which would further enable one skilled in the art on how to use the compounds for their intended use.

In the Office Action, the Examiner states that "... the applicant has not sufficiently shown *sufficient data* in the specification that the claimed compounds can treat chronic inflammation with great efficacy" [emphasis added]. Applicants submit that, in making the rejection of the claims for lack of enablement, the Examiner has focused on the absence of test data and in so doing has equated such absence with the absence of working examples, a factor to be considered in examining the application (*In re Wands*, 8 USPQ2d 1400).

However, according to the Training Materials, a statement in the specification that an assay was conducted using compounds of the invention and that the compounds were active in at least one assay constitutes the presence of "working examples", even without specific data, if the assays are reasonably correlative to the claimed utility of the compounds sought to be patented. The assays disclosed in the specification are clearly reasonably correlative to the claimed utility. It was known at the time of the invention that microglia secrete a large number of autotoxic products that generate or mediate inflammation, as discussed in the Background of the Invention. This knowledge in the art coupled with the assays disclosed in the Examples, which include both *in vitro* and *in vivo* tests, are designed to detect and measure inhibition of microglia activation. All of these assays are clearly related to the use of the compounds as inhibitors of microglia activation and in treating diseases characterized by activated microglia such as chronic inflammation, and, as stated in the specification, the compounds of the invention were active in the assays.

As the Training Materials further state:

> "It **is proper** to accept as being true the statement that the [compounds] were active in the assays, **even in the absence of specific data.** The Office must accept as being true the statements supporting enablement unless there is an *objective* reason, **supported with documentary evidence**, to question them, i.e., the burden is on the Office to demonstrate that there is an objective reason, supported by documentary evidence, to question the statement." [emphasis added]

Based on the measured activity of the disclosed compounds, Applicants have drafted claims to encompass what they believe to be the diseases and disorders reasonably expected to be treatable by inhibitors of microglia activation. As case law makes abundantly clear, unless the Examiner can offer actual proof to the contrary, the Examiner must accept the Applicants' statement as true that they reasonably expect compounds within the scope of the claims to serve as potential therapeutic agents for the claimed diseases and disorders. The Examiner has failed to provide such proof based on objective evidence, and instead merely points to the general proposition that various disorders have (or could have) various causative agents and involve different cellular mechanisms. This basic observation is insufficient to carry the burden of properly supporting the 35 U.S.C. §112, 1¶ rejection. The Examiner has failed to offer any specific proof that the compounds within the scope of the claims would not be expected to exhibit any therapeutic value.

Further, the Examiner's rejection also appears to be largely based on an incorrect interpretation of the "*utility*" standard under the Patent Act, as evidenced by the Examiner's statement that "... the applicant has not sufficiently shown sufficient data in the specification that the claimed compounds can treat chronic inflammation with *great efficacy*" [emphasis added]. Indeed, the Examiner's interpretation was squarely rejected by the U.S. Court of Appeals for the Federal Circuit in *In re Brana*, 34 USPQ 2d 1436 (Fed. Cir. 1995).

As stated above, the Applicants' Specification must be taken to be in compliance with §112 unless the Examiner provides a supported reason to doubt otherwise:

> "A specification ... *must* be taken as in compliance with the enabling requirement of the first paragraph of §112 *unless* there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support."

In re Brana, 34 USPQ 2d at 1441 [emphasis in original]. As in the present case, the decision in *In re Brana* involved the USPTO improperly second-guessing the utility of claimed pharmaceutical compounds on the basis that pre-clinical testing of the compounds does not

provide any definitive proof that the compounds could actually be used to treat any disorder. The Court clearly rejected this approach stating:

> "Usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans. Were we to require Phase II testing in order to prove utility, the associated costs would prevent many companies from obtaining patent protection on promising new inventions, thereby eliminating an incentive to pursue, through research and development, potential cures in many crucial areas ...."

In re Brana, 34 USPQ 2d at 1443 (citations omitted). As made perfectly clear by this decision, patent claims to pharmaceutical inventions can cover "potential cures" – not just compounds where safety and efficacy has been clearly and definitively established. *Id.* As in *Brana*, where the basis for the USPTO's §112, 1¶ rejection is merely a vague asserted doubt in the predictive nature of the Applicants basis for claiming utility: "applicants should not have been required to substantiate their presumptively correct disclosure to avoid a rejection under the first paragraph of §112." *In re Brana* at 1441.

Applicants have provided more than a reasonable link between the activity of the claimed compounds and the claimed utilities of these compounds. Notwithstanding the Examiner's general observation as to the predictability of finding effective drugs for various disorders and also the Examiner's apparent requirement that all the claimed compounds must have been shown to have activity (see Examiner's comments in the Office Action that "[a]n *indeterminate quantity* of experimentation would be necessary to determine all potential therapeutic compounds/compositions' effects on microglia activation" [emphasis added] to support the finding of nonenablement), Applicants have sufficiently enabled the pending method claims under the standard set forth in *In re Brana*. As *In re Brana* makes abundantly clear, the need for ongoing research and development does not negate enablement in the context of pharmaceutical inventions. Indeed such ongoing experimentation is typical in the pharmaceutical industry, and while substantial in both terms of quantity and time, does not properly qualify as **"undue"** experimentation within the pharmaceutical art. A substantial "quantity" of experimentation is not equivalent to "undue" experimentation (see, e.g., *Atlas Powder Co. v. E.I. du Pont de Nemours & Co.*, 224 USPQ 409 (Fed. Cir. 1984), where the court held that the patent specification was enabling even though it listed elements that could form thousands of end products, some of which may not even be operative). Those of skill in the art would know quite well the required steps to take based on the knowledge in the art and the teachings in the specification.

In view of the above remarks, Applicants respectfully request that the Examiner withdraw the §112, 1¶ rejection

Rejection under 35 U.S.C. §112, 2¶

The Examiner has rejected claim 43 under 35 U.S.C. §112, 2¶, stating that there is insufficient antecedent basis for the limitation to specific diseases.

While Applicants disagree with this rejection, in view of the cancellation of claim 43, the rejection is now moot. The rejection will be addressed when and if it is raised in a continuing application.

Rejections under 35 U.S.C. §102(b)

(1) The Examiner has rejected claim 43 under 35 U.S.C. §102(b) as being anticipated by Lunn et al. (Hcaplus 125:300996 USP 5,552,426), stating that Lunn discloses the instant method of treating conditions associated with β-amyloid peptide with the compound RN 175714-04-2.

While Applicants disagree with this rejection, in view of the cancellation of claim 43, the rejection is now moot. The rejection will be addressed when and if it is raised in a continuing application.

(2) The Examiner has rejected claims 15-24, 29, 30, 32-34, 37, 38, 40 and 42-44 under 35 U.S.C. §102(b) as being anticipated by Burns et al. (Hcaplus 124:289536; EP 694535), stating that Burns discloses the instant method of treating inflammatory diseases with the compound RN 175714-04-2.

This rejection is respectfully traversed. It is believed that the Patent Office has not met its burden of establishing a *prima facie* case of anticipation. Anticipation requires the disclosure in a single prior art reference of each element of the claim under consideration (*W.L. Gore & Associates v. Garlock, Inc.*, 220 USPQ 303, at 313 (Fed. Cir. 1983)). There must be no difference between the claimed invention and the reference disclosure (*Scripps Clinic & Research Foundation v. Genentech Inc.*, 18 USPQ 2d 1001, at 1010 (Fed. Cir. 1991)).

Compound RN 175714-04-2 in Burns et al. has the moiety $-CH(NHCH_2CH_3)-CH_3$ at the 5-position on the benzimidazole. However, such a moiety, as a substituent at any position on the benzimidazole, is neither disclosed nor claimed in the present invention. Further, the substituents on the benzimidazole ($-R^3$ and –Y–A–B) claimed in the present invention are

themselves nowhere disclosed in the Burns et al. EP patent publication corresponding to Hcaplus124:289536. Therefore, there can be no anticipation, and it is requested that this rejection be withdrawn.

It is noted that claims 26, 35 and 36 are not included within this rejection. While claims 35 and 36 have been cancelled, the compounds encompassed therein are also encompassed in new claims 45-48, which claims are also not anticipated by Burns et al.

Rejections under 35 U.S.C. §103(a)

(1) The Examiner has rejected claim 43 under 35 U.S.C. §103(a) as being unpatentable over Lunn et al. (USP 5,552,426) in view of Hcaplus 122:236400.

While Applicants disagree with this rejection, in view of the cancellation of claim 43, the rejection is now moot. The rejection will be addressed when and if it is raised in a continuing application.

(2) The Examiner has rejected claims 15-24, 29, 30, 32-34, 37, 38, 40 and 42-44 as being anticipated by Bruns [sic] et al. (EP 694535) [it appears that "Bruns" is a misprint on the EP publication, as the publication corresponds to Burns et al., Hcaplus 124:289536]. In particular, the Examiner states that "[t]he difference between the prior art method and the instantly claimed method is the teaching of a method of treating with a genus versus subgenus of compounds as disclosed in the prior art. It would have been obvious to one of ordinary skill in the art to select various known radicals within a genus to prepare structurally similar compounds and to use these compounds to treat the claimed diseases."

Applicant respectfully traverses this rejection; the Examiner has not made out a case of *prima facie* obviousness.

It is well-settled that in considering obviousness under 35 USC §103, the prior art as a whole must be considered and its teachings must be viewed as they would have been by one of skill in the art at the time of the invention. To properly support a rejection based upon *prima facie* obviousness, the Examiner must cite to a combination of prior art references which sets forth the necessary elements of the claimed invention ***and*** which provides the motivation for combining those elements to yield the claimed invention. *See, e.g., Northern Telecom Inc. v. Datapoint Corp.*, 15 USPQ2d 1321, 1323 (Fed. Cir. 1990). The Federal Circuit has required that specific support must be found in the prior art that "suggests" or "teaches" the modification necessary to resolve the differences of the prior art with a claimed invention. *In re Grabiak*,

226 USPQ 870 (Fed. Cir. 1985). If either the necessary elements of the invention or the motivation to combine such elements is missing, the Examiner cannot properly support the rejection based upon 35 USC §103 and it must be withdrawn.

When, as here, there is only a single reference cited, the Federal Circuit has noted that "[e]ven when obviousness is based on a single prior art reference, there must be a showing of a suggestion or motivation to modify the teachings of that reference" (*In re Kotzab*, 55 USPQ2d 1313, 1316-17 (Fed. Cir. 2000); see also *SIBIA Neurosciences, Inc. v. Cadus Pharmaceutical Corp.*, 55 USPQ2d 1927, 1931 (Fed. Cir. 2000)).

Applicant respectfully submits that the obviousness rejection is improper for two reasons. First, there is ***no*** suggestion or motivation in this one prior art reference to combine its teachings to carry out the claimed invention. Second, even if, *arguendo*, the reference could possibly be interpreted as suggesting their combination, the reference cited by the Examiner ***fails*** to set forth necessary elements of the claimed invention.

Contrary to the Examiner's interpretation, the compounds disclosed by Burns et al. are ***not*** a subgenus of the genus claimed in the present invention. As just one example, the $-R^3$ substituent of Burns, which corresponds to the –Y–A–B group of the invention, is completely outside the scope of the substituents claimed for the –Y–A–B group. The claimed –Y–A–B group is neither taught nor suggested in Burns et al. Thus, there is no suggestion whatever that the –Y–A–B group of the invention should be substituted for the $-R^3$ substituents of Burns, and there is certainly no motivation to combine the teachings in Burns to get the –Y–A–B group since, in fact, Burns does not in any way teach such a group. Burns et al. fail to set forth a necessary element, the –Y–A–B group, of the claimed invention. Therefore, the claims are not obvious in view of Burns et al. EP 694535.

It is noted that claims 26, 35 and 36 are not included within this rejection. While claims 35 and 36 have been cancelled, the compounds encompassed therein are also encompassed in new claims 45-48, which claims are also not obvious in view of Burns et al.

In view of the above remarks, Applicants respectfully request that the Examiner withdraw this §103(a) rejection.

Conclusion

Applicants respectfully submit that the instant application is now in condition for allowance. Such action is earnestly solicited at an early date.

We believe that no fee is due, however, Commissioner is hereby authorized to charge deposit account #02-2117 for any fees required to facilitate the filing of this application and/or credit any overpayments. However, this is not authorization to charge the issue fee.

Respectfully submitted,

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Date: Dec. 12, 2005

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